BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Robert H. Costa	**Professor of Biochem. & Molecular Genetics**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Arizona, Tucson		1977	Biology and Chemistry
University of California, Irvine	B.S.	1980	Biology and Chemistry
University of California, Irvine: Dr. Edward K. Wagner	**Ph.D.**	1985	**Molecular Virology**
Rockefeller University, NY: Dr. James E. Darnell, Jr.	**Postdoc.**	1988	**Liver Gene Transcription**

NOTE: The Biographical Sketch may not exceed four pages. Items A and B may not exceed two of the four-page limit.

A. **Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

1989 – 2000 Assistant and Associate Professor of Molecular Biol. and Biochem, University of Illinois at Chicago.
2000 – Pres. Professor of Biochemistry & Molecular Genetics, University of Illinois at Chicago.
1993 – 1998 Established Investigator Award: Salary Grant from the AHA / Bristol-Myers Squibb.
2000 – Pres. Member, NIH Metabolic Pathology Study Section. (Now called Tumor Cell Biology – October 2003).
2001 – Pres. Editorial Board for the Journals: Hepatology and Gene Expression
2003 – Pres. Editorial Board for the Journal of Biological Chemistry

B. **Selected peer-reviewed publications (in chronological order).** Do not include publications submitted or in preparation. Publications: **(Selected from 82 peer-reviewed manuscripts)**

1. Ye. H., T. Kelly, L. Lim, U. Samadani, S. Rubio, D. G. Overdier, and **R. H. Costa**. (1997). Hepatocyte nuclear factor-3/fork head homolog-11 is expressed in proliferating mesenchymal and epithelial cells of embryonic and adult tissues. **Molecular Cellular Biology 17:**1626-1641.
2. Rausa, F., U. Samadani, H. Ye, L. Lim, C. Fletcher, N. A. Jenkins, N. G. Copeland and **R. H. Costa**. (1997). The cut-homeodomain transcriptional activator HNF-6 is co-expressed with its target gene HNF-3beta in the developing murine liver and pancreas. **Developmental Biology 192:** 228-246.
3. Ye, H., A. X. Holterman, R. R. Franks, and **R. H. Costa**. (1999). Premature expression of the winged helix transcription factor HFH-11 in regenerating mouse liver accelerates hepatocyte entry into S-phase. **Molecular Cellular Biology 19:** 8570-8580.
4. Gannon, M., M. K. Ray, K. Van Zee, F. M. Rausa, **R. H. Costa** and C. V. Wright. (2000). Persistent expression of HNF-6 in islet endocrine cells causes disrupted islet architecture and loss of beta cell function. **Development. 127:** 2883-2895.
5. Rausa, F. M., Y. Tan, H. Zhou, K. Yoo, D. B. Stolz, S. Watkins, R. R. Franks, T. G. Unterman and **R. H. Costa**. (2000). Elevated levels of HNF-3beta in mouse hepatocytes influence expression of genes involved in bile acid and glucose homeostasis. **Molecular Cellular Biology 20:** 8264-8282.
6. Kalinichenko, V.V., L. Lim, B. Shin, and **R. H. Costa**. (2001). Differential expression of forkhead box transcription factors following butylated hydroxytoluene lung injury. **American J. Physiology Lung Cellular and Molecular Physiology 280:** L695-L704.
7. Wang, X., N.-J. Hung and **R. H. Costa.** (2001). Earlier expression of the transcription factor HFH 11B (FOXM1B) Diminishes Induction of p21CIP1/WAF1 levels and accelerates mouse hepatocyte entry into S-phase during carbon tetrachloride induced liver regeneration. **Hepatology 33:** 1404-1414.
8. Kalinichenko, V.V., L. Lim, D. Beer-Stoltz, B. Shin, F. M. Rausa, J. Clark, J. A. Whitsett, S. C. Watkins and **R. H. Costa.** (2001). Defects in Pulmonary Vasculature and Perinatal Lung Hemorrhage in Mice Heterozygous Null for the *Forkhead Box f1* transcription factor. **Developmental Biology 235:** 489-506.
9. Wang, X., E. Quail, N.-J. Hung, Y. Tan, H. Ye and **R. H. Costa.** (2001). Increased Levels of Forkhead Box M1B Transcription Factor in Transgenic Mouse Hepatocytes Prevents Age-Related Proliferation Defects in Regenerating Liver. **Proc. Natl. Acad. Sci. USA. 98:** 11468-11473.

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10. Nag, A., A. Datta, K, Yoo, D. Bhattacharyya, A. Chakrabortty, X. Wang, B. L. Slagle, **R. H. Costa**, and P. Raychaudhuri. (2001). DDB2 Induces Nuclear Accumulation of the Hepatitis B Virus X Protein Independently of DDB1. **J. Virology 75:** 10383-10392.
11. Yu, S. W-Q Cao, P. Kashireddy, K. Meyer, Y. Jia, D. E. Hughes, Y. Tan, **R. H. Costa**, J. Feng, A. V. Yeldandi, M. S. Rao, F. J. Gonzalez, and J. K. Reddy. (2001). Human peroxisome proliferator-activated receptor alpha (PPARalpha) supports the induction of peroxisome proliferation in PPARalpha deficient mouse liver. **J. Biol. Chem. 276:** 42485-42491.
12. Tan, Y., D. E. Hughes, X. Wang and **R. H. Costa.** (2002). Adenovirus-Mediated Hepatic Increase in HNF-3beta or HNF-3alpha shows differences in levels of liver glycogen and gene expression. **Hepatology. 35:**30-39.
13. Lim, L., V. V. Kalinichenko, J. A. Whitsett and **R. H. Costa**. (2002). Fusion of right lung lobes and pulmonary vessels in mice heterozygous for the *Forkhead Box f1* targeted allele. **American J. Physiology Lung Cellular and Molecular Physiology 282:**L1012-L1022.
14. Kalinichenko, V.V., Y. Zhou, B. Shin, D. Beer-Stoltz, S. C. Watkins, J. A. Whitsett, and **R. H. Costa.** (2002). Wild Type Levels of the Mouse *Forkhead Box f1* Gene are Essential for Lung Repair. **American J. Physiology Lung Cellular and Molecular Physiology 282:**L1253-L1265.
15. Tan, Y., G. Adami and **R. H. Costa.** (2002). Maintaining HNF-6 expression prevents AdHNF3beta Mediated decrease in hepatic levels of Glut2 and glycogen. **Hepatology 35:**790-798.
16. Kalinichenko, V.V., Y. Zhou, D. Bhattacharyya, W. Kim, B. Shin, K. Bambal and **R. H. Costa**. (2002). Haploinsufficiency of the Mouse *Forkhead Box f1* gene causes Defects in Gall Bladder Development. **J. Biol. Chem. 276:** 42485-42491.
17. Guo, Y., **R. Costa,** H. Ramsey, T. Starnes, G. Vance, K. Robertson, M. Kelley, R. Reinbold, H. Scholer, and R. Hromas. (2002). The embryonic stem cell transcription factors Oct-4 and FoxD3/Genesis interact to regulate endodermal-specific promoter expression. **Proc. Natl. Acad. Sci USA. 99:**3663-3667.
18. Holterman, A. X., Y. Tan, W. Kim, K. Yoo and **R. H. Costa.** (2002). Diminished hepatic expression of the HNF- 6 transcription factor following bile duct obstruction. **Hepatology 35:**1392-1399.
19. Chen, Y., R. Sharma, **R. H. Costa,** E. Costa and D. R. Grayson. (2002). On the epigenetic regulation of human reelin promoter. **Nucleic Acids Research: 30:** 2930-2939.
20. Wang, X., K. Krupczak-Hollis, Y. Tan, G. R. Adami and **R. H. Costa.** (2002). Increased Hepatic FoxM1B Levels in Old-Aged Mice Stimulated Liver Regeneration through Diminished $p27^{Kipl}$ Protein Levels and Increased Cdc25B Expression. **J. Biol. Chem. 277**:44310-44316.
21. Banks, K. E., A. L. Anderson, H. Tang, D. E. Hughes, **R. H. Costa** and A. McLachlan. (2002). Hepatocyte Nuclear Factor 3β Inhibits Hepatitis B Virus Replication *In Vivo*. **J. Virology. 76:**12974-12980.
22. Wang X., H. Kiyokawa, M. B. Dennewitz and **R. H. Costa.** (2002). The Forkhead Box m1b Transcription Factor is Essential for Hepatocyte DNA Replication and Mitosis during Mouse Liver Regeneration. **Proc. Natl. Acad. Sci USA., 99:**16881-16886.
23. Rausa, F., Y. Tan and **R. H. Costa.** (2003). Association between the FoxA2 and HNF-6 DNA binding domains stimulates FoxA2 transcriptional activity but inhibits HNF-6 DNA binding. **Molecular Cellular Biology. 23:**437-449.
24. Kalinichenko, V. V., D. Bhattacharyya, Y. Zhou, G. A. Gusarova, W. Kim, B. Shin, and **R. H. Costa.** (2003). *Foxf1* +/- Mice Exhibit Defective Stellate Cell Activation and Abnormal Liver Regeneration Following CCl_4 Injury. **Hepatology, 37:**107-117.
25. Kalinichenko, V. V., G. A. Gusarova, B. Shin, and **R. H. Costa.** (2003). The Forkhead Box F1 Transcription Factor is Expressed in Brain and Head Mesenchyme during Mouse Embryonic Development. **(Mechanisms of Development) Gene Expression Patterns 3:** 153-158.
26. Hughes, D. E., D. Beer-Stoltz, S. Yu, J. K. Reddy, S. C. Watkins, A. M. Diehl and **R. H. Costa.** (2003). Elevated Hepatocyte Levels of Foxa2 (HNF-3beta) Cause Postnatal Steatosis and Mitochondrial Damage. **Hepatology. 37:**1414-1424 (Cover of Journal).
27. Kalinina, O. A., S. A. Kalinin, E. W. Polack, I. Mikaelian, S. Panda, **R. H. Costa** and G. R. Adami. (2003). Sustained hepatic expression of FoxM1B in transgenic mice has minimal effects on hepatocellular carcinoma development but increases cell proliferation rates in pre-neoplastic and early neoplastic lesions **Oncogene. In Press.**
28. Kalinichenko, V. V., G. A. Gusarova, I-M Kim, B. Shin, Y. Tan, I-C Wang, M. L. Major, X. Wang and **R. H. Costa.** (2003). Ubiquitous Expression of the Forkhead Box M1B Transgene Accelerates Proliferation of Distinct Pulmonary Cell-Types Following Lung Injury. **Journal of Biol. Chem., In press. Jul 16.**
29. Krupczak-Hollis, K., X. Wang, M. B. Dennewitz, and **R. H. Costa.** (2003). Growth Hormone Stimulates Proliferation of Old-aged Regenerating Liver Through Forkhead Box m1b. **Hepatology. In revision.**

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C. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

COSTA, R.H.

ONGOING

1 RO1 AG021842-01 Costa (PI)

01/01/03 – 12/31/07

NIH/NIA

FoxM1B Protein in Stimulating Proliferation during Aging

The major goals of this project are to use the interferon inducible Mx-Cre recombinase transgene to conditionally delete the *Foxm1b* gene in young adult mice to test the hypothesis that extinguishing FoxM1B expression in all proliferating cells will lead to defective cellular proliferation and premature aging. We will use the Rosa26 promoter FoxM1B transgenic mice to test the hypothesis that maintaining FoxM1B levels in all cell-types will alleviate proliferation defects associated with aging and lead to life span extension.

3 RO1 GM43241-14 Costa (PI)

07/01/03 – 06/30/07

NIH/NIGMS

Regulation of Transthyretin in the Liver

The major goals of this project are to characterize the mechanisms and signaling pathways regulating HNF6-FoxA2 transcriptional synergy and further characterize the synergistic transcriptional activation of HNF-6 by C/EBPα. We plan to examine *in vivo* protein binding of the transcription factors regulating TTR and HNF-3β promoter expression using Chromatin Immunoprecipitation (ChIP) assay. We will examine conditional hepatocyte expression of a HNF-6 dominant negative (DN) transgene protein which disrupts HNF6-FoxA2 transcriptional synergy. We will develop transgenic mice that conditionally express a FoxA1 DN protein to determine the role of Foxa transcription factors in liver development and function.

1 RO1 DK54687-05 Costa (PI)

03/01/99 – 02/29/04

NIH/NIDDK

Hepatocyte Nuclear Factors in Liver Regeneration

The major goals of this project are to examine whether premature hepatocyte expression of proliferation-specific Forkhead Box M1B (FoxM1B previously called HFH-11B) transcription factor in transgenic mice accelerates cell-cycle kinetics of proliferating hepatocytes during liver regeneration. We will also generate mice possessing a conditional targeted *FoxM1B* gene disruption in adult hepatocytes to examine whether FoxM1B expression is necessary for hepatocyte replication during liver regeneration.

PENDING

2 RO1 DK54687-06 Costa (PI)

03/01/04 – 02/29/09

NIH/NIDDK

Hepatocyte Nuclear Factors in Liver Regeneration

Competitive renewal: Diminished hepatocyte DNA replication and mitosis in regenerating Albumin Cre recombinase (Alb-Cre) *Foxm1b* -/- liver was associated with increased levels of the cyclin dependent kinase (Cdk) inhibitor $p21^{Cip1}$ protein and undetectable expression of Cdc25B phosphatase protein required for activation of M-phase promoting Cdk1. We will test the hypothesis that deleting the $p21^{Cip1}$ gene and restoring Cdc25B expression will increase hepatocyte proliferation in regenerating Alb-Cre *Foxm1b* -/- liver. We have deleted the *Foxm1b* allele in early embryonic liver and will further characterize the severe defect in liver development. We will test the hypothesis that Alb-Cre *Foxm1b* -/- hepatocytes are refractory to developing hepatocellular carcinoma in response to a Diethylnitrosamine (DEN) /Phenobarbital liver tumor induction protocol.

COMPLETED

1 RO1 HL62446-04 Costa (PI)

04/01/99 – 03/31/03

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NIH/NHLBI

HFH-8 (Foxf1) in Lung Morphogenesis and Endothelial Function

The major goals of this project are to use Forkhead Box f1 -/- (Foxf1, HFH-8) mice to examine its role in mesenchyme induction of lung morphogenesis and pulmonary endothelial cell function. The Foxf1 deficient lungs will be used to identify Foxf1 target genes via differential hybridization of cDNA microarrays.

OVERLAP

There is no overlap between the current NIH application and the Ongoing NIH grant and the pending NIH competitive renewal applications.

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